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Comment on: Screening for malignant melanoma—a critical assessment in historical perspective

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In his opinion piece, Wolfgang Weyers (2018) suggests that the practice of biopsying small lesions (<6 mm in diameter) without conspicuous clinical and/or dermoscopic features of melanoma is a key contributing factor to the so-called epidemic of melanoma overdiagnosis. He contends that these clinically non-diagnostic lesions often lack histopathologic criteria that allow precise classification, which leads to false-positive diagnoses. He proposes delaying biopsy of lesions that are suspicious, but not diagnostic, for melanoma until features consistent with malignancy arise, the aim being to decrease diagnostic and biologic uncertainty and thereby minimize the potential for melanoma overdiagnosis together with its associated cost and morbidity. The view expressed by Dr. Weyers is intriguing, and the overarching concept raises important questions relevant to the diagnosis of melanoma.

1. **What is the optimal sensitivity and specificity threshold for melanoma diagnosis?** While taking a watch-and-wait approach until melanoma unequivocally declares itself will increase specificity and possibly decrease the likelihood of overdiagnosis, this approach implies a concomitant decrease in sensitivity for melanoma detection. This, in turn, may result in some individuals developing advanced stage melanomas due to the missed opportunity of early detection. This is not an uncommon scenario occurring in patients with difficult to detect melanoma subtypes, such as nodular, desmoplastic, nevoid, amelanotic, or spitzoid melanoma. Further research is needed to determine if the benefits of a reduction in overdiagnosis and unnecessary biopsies outweigh the harm that may result from missed early melanoma detection.
2. **Which patient population is most amenable to watchful waiting of suspicious but not overtly malignant lesions?** The concept of waiting until melanoma declares itself before performing a biopsy is contingent upon (a) patient and physician acceptance of monitoring as a reasonable choice, and (b) patient vigilance and periodic physician based follow-up. Regarding the former, the idea of observing a suspicious lesion that may be an early melanoma may not be acceptable to certain patients, such as those with significant anxiety, a personal history of melanoma, or a family history of lethal melanoma. In some countries, the practice may also be associated with increased legal liability to the physician. Regarding the latter, although there are some patients who are meticulous about regularly examining their skin, others lack the needed confidence or are unwilling or unable to consistently perform self-examinations. Even if patients are monitoring their own skin, the ability to detect subtle (and occasionally seemingly obvious) changes indicative of melanoma progression is not always possible. Finally, a significant number of patients fail to keep their follow-up appointments, and some of these patients may go on to develop aggressive melanomas.
3. **How are small equivocal lesions best monitored?** To some extent, the concepts alluded to by Dr. Weyers are already implemented in clinical practice. Total body photography

(TBP) and digital dermoscopic monitoring is one standard of care used in many clinics that screen patients at high risk for melanoma. The aim of digital monitoring is to actively follow banal and equivocal flat lesions with the aim of biopsying only those lesions that are changing in a concerning manner. However, while this time- and cost-intensive approach can improve the yield for diagnosis of melanoma, in our experience it does not always eliminate the biopsy of lesions that prove to be histopathologically equivocal. In fact, borderline lesions and nevi with unusual features appear to be enriched. Among biologically dynamic, small, equivocal lesions, how certain do we need to be before performing a biopsy? If our threshold is too high, some patients may die from advanced disease because lesions were not biopsied at an earlier point in time. In practical terms, however, TBP and digital dermoscopic monitoring are not always available to patients, and the best approach to monitoring lesions without access to these technologies remains unclear.

4. **What is the most appropriate interval for follow-up, and until what time point should small equivocal lesions be monitored?** Based on currently available data, there are no clear answers to these questions.
5. **Finally, does the removal of small equivocal lesions truly result in the overdiagnosis of melanoma?** It is worth highlighting that there is no solid evidence and no study referenced to support Dr. Weyers' claim that dermatopathologists' interpretation of smaller lesions contributes to overdiagnosis. In fact, the opposite may be true. Since most small lesions are captured in their entirety by a biopsy, all available diagnostic criteria can be applied, and if needed, modern ancillary methods are available to support the correct diagnosis. Furthermore, most pathologists hesitate to establish a diagnosis of melanoma because of the small diameter of a lesion and usually render a diagnosis of melanoma only if there is compelling evidence from microscopic review (e.g., marked asymmetry, florid and chaotic pagetoid spread, and severe atypia) or ancillary studies. The same is true for small and partial biopsies. It is not our experience that pathologists issue a diagnosis of melanoma as a default option when the diagnosis is difficult; instead, they usually admit diagnostic uncertainty. While the biopsy of small lesions and small partial biopsies of lesions have undoubtedly contributed to an inflation of descriptive pathology reports (e.g., "atypical melanocytic proliferation"), such evasive diagnoses should not enter melanoma statistics and therefore cannot be responsible for the increase in the reported incidence of melanoma.

We agree with Dr. Weyers that wholesale biopsy (especially partial biopsies) of small, non-palpable, equivocal lesions should be discouraged. We also agree that if a lesion has compelling clinical or dermoscopic features for melanoma, then a biopsy should be performed, irrespective of the lesion's diameter. However, while there are benefits to the watch-and-wait approach for small equivocal lesions as outlined by Dr. Weyers, there are also potential pitfalls and unanswered questions that require further study. We posit that a combined approach using morphologic (clinical examination, dermoscopy, confocal microscopy, etc.), comparative (e.g., ugly duckling sign), temporal (monitoring using TBP, dermoscopy, confocal microscopy), and genomic data (e.g., non-invasive molecular assays obtained via microbiopsies, tape-stripping, etc.), augmented someday by machine learning approaches, will likely address some of the core issues described in the opinion piece by Dr. Weyers. Furthermore, as our understanding of the biology of melanocytic neoplasms continues to expand, the prevalence of lesions with diagnostic and biologic uncertainty will decrease, but complete knowledge of the potential nature of every lesion over the course of each individual's life will, of course, remain elusive.